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| Complete List of Authors: | Jia, Yitong; Xuanwu Hospital Capital Medical University, Anesthesiology<br>wang, zheng; Xuanwu Hospital Capital Medical University, Department of General Surgery<br>Ma, Yanhui; Xuanwu Hospital Capital Medical University, Anesthesiology<br>Wang, Tengteng; Xuanwu Hospital Capital Medical University, Thoracic Surgery<br>Feng, Kunpeng; Xuanwu Hospital Capital Medical University, Anesthesiology<br>Feng, Guang; Xuanwu Hospital Capital Medical University, Anesthesiology<br>Wang, Tianlong; Xuanwu Hospital Capital Medical University |
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# Efficacy and safety of high-voltage pulsed radiofrequency versus standard-voltage pulsed radiofrequency for patients with neuropathic pain: protocol for a systematic review and meta-analysis

[1,2]Yitong Jia, [3]Zheng Wang, [1,2]Yanhui Ma, [4]Tengteng Wang, [1,2]Kunpeng Feng, [1,2]Guang Feng [1,2]Tianlong Wang

[1]Department of Anesthesiology, Xuanwu Hospital, Capital Medical University, Beijing, China.
[2]Beijing Municipal Geriatric Medical Research Center, Beijing, China.
[3]Department of General Surgery, Xuanwu Hospital, Capital Medical University, Beijing, China.
[4]Department of Thoracic surgery, Xuanwu Hospital, Capital Medical University, Beijing, China.

Correspondence to
Prof Tianlong Wang, Department of Anesthesiology, Xuanwu Hospital, Capital Medical University, Beijing, China; E-mail: w_tl5595@hotmail.com.

Yitong Jia, Zheng Wang and Yanhui Ma contributed equally to this paper.



## Abstract

**Introduction** Pulsed radiofrequency (PRF) is commonly used for the treatment of neuropathic pain (NP). However, whether increasing the output voltage of PRF can safely improve the efficacy of PRF treatment remains unclear. This study aims to compare the efficacy and safety of high-voltage PRF and standard-voltage PRF for the treatment of patients with NP.

**Methods and analysis** We will search PubMed/MEDLINE, EMBASE, Web of Science, and the Cochrane Library (from the date of inception until March 15, 2022), etc. Only randomized controlled trials (RCTs) will be included. Two reviewers (YJ and GF) will independently complete the study screening and selection, data extraction, risk of bias assessment, and quality of evidence assessment. The primary outcome of this meta-analysis will be the efficiency rate in patients with NP. The secondary outcomes will include numeric rating scale (NRS), visual analog scale (VAS) score, time to take effect, rescue drug dosage, quality of life (QoL) using the health questionnaire (SF-36), and the incidence of adverse events (AEs). Meta-analyses will be conducted using standard meta-analysis software (RevMan V.5.3, The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark).

**Ethics and dissemination** Ethical approval was waived as our systematic review will be based on published literature. The results of this study will be submitted to a peer-reviewed journal.

**PROSPERO registration number** CRD42022297804.

**Strengths and limitations of this study**

To our knowledge, this will be the first systematic review and meta-analysis to evaluate the efficacy and safety of high-voltage PRF for the treatment of patients with NP.

Only randomized controlled trials will be included in our study to provide unbiased information than other study designs

This study findings will provide comprehensive information for future study designs in terms of interventional treatment of neuropathic pain.

The accuracy of the conclusions of our research may be subjected to language limitations for only English published studies will be included.

**Key words:** high-voltage, pulsed radiofrequency, neuropathic pain, randomized controlled trials

# Introduction

Neuropathic pain (NP) is a common chronic pain condition caused by lesions or diseases affecting the somatosensory nervous system, including trigeminal neuralgia, peripheral nerve injury pain, painful polyneuropathy, postherpetic neuralgia, central poststroke pain

and so on.[1] Epidemiological data have reported that the global prevalence of NP is approximately 6.9% - 10%.[2] NP is a refractory pain syndrome with a long duration of occurrence, frequent recurrent attacks, and poor response to traditional analgesics. Most patients with NP suffer from ongoing or intermittent spontaneous pain with burning, pricking, and a squeezing sensation with poor quality of life (QoL).[3] Therefore, finding an effective treatment option for NP and improving patients' QoL is of great importance. In recent years, pulsed radiofrequency (PRF), a new type of neuromodulation technique, has been successfully applied in the treatment of NP.[4-9]. Different from continuous radiofrequency (CRF), which produces heat by friction and vibration, leading to thermocoagulation, denaturation, and necrosis of the target tissue, PRF provides pulsed energy waves followed by a 480 ms heat dissipation interval, and the temperature does not exceed 42°C.[10 11] The mechanism of PRF treatment is via the modulation of nerve function caused by the electric field effect rather than blocking pain signal transduction.[12 13] Thus, PRF is a nondestructive technique that can be repeatedly applied without damage to nerve tissue.[11]

The standard proposed PRF parameters were set as an output voltage of 45 V, temperature of 42 °C, pulse frequency of 2 Hz, output frequency of 500 kHz, continuous current action of 20 ms, and intermission period of 480 ms. Recently, scholars have attempted to treat NP patients with high-voltage PRF. Teixeira and Sluijter first reported that high voltage PRF of 60 V on discogenic pain patients attained satisfactory efficacy over 3 months.[14] In 2013, Luo et al found that the postoperative numeric rating scale (NRS) was

significantly negatively correlated with the output voltage of PRF.[15] Moreover, Luo et al also compared the efficacy of high voltage PRF and standard voltage PRF for refractory neuralgia infraorbital nerve therapy, and results revealed that high voltage PRF could achieve higher response rates at month 1, 3 months, 6 months, and one year post-procedure.[16] However, more patients in the high-voltage group (27%) experienced mild numbness postoperatively than in the standard-voltage group (13%). In addition, a randomized controlled trial (RCT) conducted by Wan et al showed that the scores were significantly lower in the high-voltage group than in the standard-voltage group at 3 and 6 months, but with no significant difference was observed at one month after treatment.[17] In addition, Wan et al 's results revealed that the incidence of ecchymoses in the high-voltage group (19.2%) was higher than that in the standard-voltage group (12.1%). As a result, whether the efficacy of high-voltage PRF at different time points is superior to that of standard-voltage PRF, and whether high-voltage PRF is a safe treatment method requires further analysis.

The primary objectives of this study will be to compare the efficacy and safety of high-voltage PRF and standard-voltage PRF for the treatment of NP at different time points postoperatively through a systematic review and meta-analysis of RCTs.

# Methods

This protocol was developed according to the reporting guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P)

statement[18] **(checklist in Supplement 1).** The protocol for this systematic review was registered in the PROSPERO database (registration number: CRD42022297804). Our systematic review will be conducted in accordance with the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions.[19] Any amendments made to this protocol and the whole review process will be updated in a timely manner on the PROSPERO registration and the final manuscript.

## Criteria for considering studies for this review

### Types of studies

Only RCTs will be included. All studies must be published in English. Experimental animal studies will be excluded.

### Participants

Patients with NP conditions recognized and defined by the International Association for the Study of Pain (IASP)[20] will be included. NP is initiated or caused by a primary lesion or dysfunction of the nervous system. Studies regarding diabetic neuropathy, complex regional pain syndrome type I, low back pain without radicular pain, and postsurgical pain will be excluded.

### Interventions and Comparators

We will examine trials investigating high voltage PRF treatment for patients with NP.

The high voltage PRF treatment mode will be set as a manual pulse mode: the initial voltage was 40 or 45 V, and the output voltage will then be gradually increased to the highest voltage the patient can tolerate (temperature control below 50 °C). The comparator will be the standard PRF treatment.

**Outcome measures**

The primary outcome of this meta-analysis is the efficiency rate in patients with NP. The predefined time points for the efficiency rate will be 1 month, 3 months and 6 months after the procedure. Other time points, such as 1-year or 2-years, will also be considered. Treatment efficiency recurrence is defined as a pain reduction of greater than 50% after treatment compared to pre-surgery. Secondary outcomes will include (NRS) or visual analog scale (VAS) score, time to take effect, rescue drug dosage, and quality of life (QoL) using the health questionnaire (SF-36)[21] at 1 month, 3 months, and 6 months postoperatively, and incidence of adverse events (AEs).

## Information sources and search strategy

A computer-based search strategy will be designed by an experienced librarian and revised by another expert librarian according to the Peer Review of Electronic Search Strategies checklist.[22] The primary source of literature will be the following major electronic databases: PubMed/MEDLINE, EMBASE, Web of Science, and the Cochrane Library (from the date of inception until March 15, 2022). The secondary source of

potentially relevant research includes conference proceedings for relevant abstracts, clinical trials registers (ClinicalTrials.gov), and the World Health Organization's International Clinical Trial Registry Platform (WHO ICTRP) to identify ongoing studies. The search will encompass a broad range of terms and keywords related to "high-voltage," "pulsed radiofrequency," "neuropathic pain", and "RCT". The detailed search strategy is presented in **Supplement 2.**

## Data selection and analysis

### Study Selection

The Population, Intervention, Comparison, Outcome (PICO) model[23] will be used to determine the specific criteria for selecting studies. Two reviewers (YJ and GF) will independently screen and select the relevant studies. In the initial screening, reviewers will determine whether the study could be included by screening the titles and abstracts retrieved via database searches. The full texts retained from the initial selection of articles will be screened to include studies that meet the eligibility criteria. Disagreements between the two reviewers will be resolved by a third reviewer (TW). If several studies present data from the same study population or multiple publications from the same study are published in chronological order, the study with the most direct interventions or the largest sample size will be reserved. The same methods will be used for citation, reference screening, and selection, as well as for protocols registered in clinical trial registries.

## Data extraction

A standardized electronic form for data extraction will be created by ZW. Two reviewers (YJ and GF) will independently extract the following data: study characteristics (e.g., name of the first author, year of publication, type of study, sample size), population characteristics (e.g., age, gender, disease duration, medical history, preoperative pain intensity, and follow-up period), and outcome data (e.g., primary and secondary outcomes and any AEs caused by PRF treatment). Similarly, a third reviewer will be required to resolve any discrepancies. We will attempt to contact the study authors by email or post for further information in case of any ambiguity or insufficient information.

## Assessment of risk of bias and quality of evidence assessment

Two reviewers (YJ and GF) will independently assess risk of bias (RoB) and discrepancies will be resolved by a third reviewer (ZW). The RoB of RCTs will be assessed according to items in the Cochrane Collaboration's tool.[19]

We will evaluate the overall quality of a body of evidence in accordance with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology[24] which examines study design, RoB, inconsistency, indirectness, and imprecision. According to the GRADE, quality of evidence will be rated as high, moderate, low, or very low.

## Data synthesis and analysis

Meta-analyses will be conducted using the standard meta-analysis software (RevMan V.5.3, The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark). We will compute standardized mean differences (SMDs) and 95% confidence intervals (CIs) for continuous outcomes, and risk ratios (RR) with 95% CI for binary outcomes. A two-tailed P value of less than 0.05 is considered statistically significant. We will assess the intervention effects between high-voltage PRF and standard-voltage PRF using pre- to post-intervention changes. When the data in the literature are expressed as medians and quartiles, we will use mathematical operations to transform them into mean and standard deviation (SD).[25 26] We will use forest plots to visualize pooled estimates and the extent of heterogeneity among studies. Heterogeneity will be assessed using the $I^2$ statistic. $I^2 > 50\%$ will indicate substantial heterogeneity, and the random-effects model will be used to analyze the outcomes; otherwise, a fixed-effect model will be applied. When heterogeneity is found, we will perform subgroup analysis according to prespecified variables, such as study design, intervention characteristics, or risk of bias. The sources of heterogeneity will be explored using sensitivity analysis. A funnel plot[27] or Egger test[28] will be used to assess publication bias.

## Patient and Public Involvement

As our study is a systematic review based on published literature, no patients will be involved in this study.

# Discussion

Several studies have evaluated the efficacy of high voltage PRF in the treatment of NP. Li et al [29] and Wan et al [17] conducted RCTs and reported that the VAS score declined significantly from the baseline levels in both groups. Moreover, the VAS score in the high-voltage PRF group was significantly lower than that in the standard-voltage PRF group at some time points but not at all follow-up periods. The eight dimensions of the SF-36 scores used to assess QoL between the two groups still require detailed assessment. To date, the incidence of AEs associated with high-voltage PRF and standard-voltage PRF group is not clear. Therefore, it is important for physicians to accumulate more high-level evidence regarding the efficacy and safety of different PRF output voltages for NP patients' therapy.

The objective of our study is to compare the efficacy and safety of high-voltage PRF and standard-voltage PRF for NP therapy and provide clinical evidence for the choice of PRF modes in clinical practice via synthesizing the existing literature. However, this study has some limitations. The sample size of the eligible RCTs was not large and the accuracy of the conclusions of our research may be biased due to language limitations, as we will only include studies published in English. Overall, the study findings will provide comprehensive information for future study designs in terms of interventional treatment of NP.

# Abbreviations

PRF, Pulsed radiofrequency; NP, neuropathic pain; RCTs, randomized controlled trials;

NRS, numeric rating scale; VAS, visual analog scale; QoL, quality of life; AEs, adverse events; RoB, risk of bias; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; SMDs, standardized mean differences; CIs, confidence intervals; RR, risk ratios.

## Ethics and dissemination

Ethical approval was waived as our systematic review will be based on published literature. The results of this study will be submitted to a peer-reviewed journal.

**Acknowledgments** The authors would like to thank the participants of the study for their cooperation.

**Contributors** YJ, ZW, TW and TW made substantial contributions to clinical study design; YJ, YM and GF made substantial contributions to manuscript preparation, editing and review; KF made contributions to English language editing; YM, KF and GF consulted about clinical issues; YJ, YM, TW and TW have given final approval of the version to be published. YJ, ZW and YM contributed equally to this work. TW is responsible as corresponding author.

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**Consent for publication** All authors consented.

**Conflicts of interest** None.

## References

1. Baron R, Binder A, Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. *The Lancet Neurology* 2010;9(8):807-19. doi: 10.1016/s1474-4422(10)70143-5 [published Online First: 2010/07/24]
2. van Hecke O, Austin SK, Khan RA, et al. Neuropathic pain in the general population: a systematic

review of epidemiological studies. *Pain* 2014;155(4):654-62. doi: 10.1016/j.pain.2013.11.013 [published Online First: 2013/12/03]

3. Colloca L, Ludman T, Bouhassira D, et al. Neuropathic pain. *Nature reviews Disease primers* 2017;3:17002. doi: 10.1038/nrdp.2017.2 [published Online First: 2017/02/17]
4. Park CH, Lee SH, Lee PB. Intradiscal Pulsed Radiofrequency Application Duration Effect on Lumbar Discogenic Low Back Pain. *Pain physician* 2020;23(5):E535-e40. [published Online First: 2020/09/25]
5. Martin DC, Willis ML, Mullinax LA, et al. Pulsed radiofrequency application in the treatment of chronic pain. *Pain practice : the official journal of World Institute of Pain* 2007;7(1):31-5. doi: 10.1111/j.1533-2500.2007.00107.x [published Online First: 2007/02/20]
6. Kim K, Jo D, Kim E. Pulsed Radiofrequency to the Dorsal Root Ganglion in Acute Herpes Zoster and Postherpetic Neuralgia. *Pain physician* 2017;20(3):E411-e18. [published Online First: 2017/03/25]
7. Shi Y, Wu W. Treatment of Neuropathic Pain Using Pulsed Radiofrequency: A Meta-analysis. *Pain physician* 2016;19(7):429-44. [published Online First: 2016/09/28]
8. Jia Y, Shrestha N, Wang X, et al. The Long-Term Outcome of CT-Guided Pulsed Radiofrequency in the Treatment of Idiopathic Glossopharyngeal Neuralgia: A Retrospective Multi-Center Case Series. *Journal of pain research* 2020;13:2093-102. doi: 10.2147/jpr.S259994 [published Online First: 2020/09/10]
9. Vuka I, Marciuš T, Došenović S, et al. Efficacy and Safety of Pulsed Radiofrequency as a Method of Dorsal Root Ganglia Stimulation in Patients with Neuropathic Pain: A Systematic Review. *Pain medicine (Malden, Mass)* 2020;21(12):3320-43. doi: 10.1093/pm/pnaa141 [published Online First: 2020/06/04]
10. Wu CY, Lin HC, Chen SF, et al. Efficacy of Pulsed Radiofrequency in Herpetic Neuralgia: A Meta-Analysis of Randomized Controlled Trials. *The Clinical journal of pain* 2020;36(11):887-95. doi: 10.1097/ajp.0000000000000867 [published Online First: 2020/07/24]
11. Wu H, Zhou J, Chen J, et al. Therapeutic efficacy and safety of radiofrequency ablation for the treatment of trigeminal neuralgia: a systematic review and meta-analysis. *Journal of pain research* 2019;12:423-41. doi: 10.2147/jpr.S176960 [published Online First: 2019/01/31]
12. Sam J, Catapano M, Sahni S, et al. Pulsed Radiofrequency in Interventional Pain Management: Cellular and Molecular Mechanisms of Action - An Update and Review. *Pain physician* 2021;24(8):525-32. [published Online First: 2021/11/19]
13. Vanneste T, Van Lantschoot A, Van Boxem K, et al. Pulsed radiofrequency in chronic pain. *Current opinion in anaesthesiology* 2017;30(5):577-82. doi: 10.1097/aco.0000000000000502 [published Online First: 2017/07/13]
14. Teixeira A, Sluijter ME. Intradiscal high-voltage, long-duration pulsed radiofrequency for discogenic pain: a preliminary report. *Pain medicine (Malden, Mass)* 2006;7(5):424-8. doi: 10.1111/j.1526-4637.2006.00138.x [published Online First: 2006/10/04]
15. Luo F, Meng L, Wang T, et al. Pulsed radiofrequency treatment for idiopathic trigeminal neuralgia: a retrospective analysis of the causes for ineffective pain relief. *European journal of pain (London, England)* 2013;17(8):1189-92. doi: 10.1002/j.1532-2149.2012.00278.x [published Online First: 2013/01/17]

16. Luo F, Wang T, Shen Y, et al. High Voltage Pulsed Radiofrequency for the Treatment of Refractory Neuralgia of the Infraorbital Nerve: A Prospective Double-Blinded Randomized Controlled Study. *Pain physician* 2017;20(4):271-79. [published Online First: 2017/05/24]
17. Wan CF, Song T. Comparison of Two Different Pulsed Radiofrequency Modes for Prevention of Postherpetic Neuralgia in Elderly Patients with Acute/Subacute Trigeminal Herpes Zoster. *Neuromodulation : journal of the International Neuromodulation Society* 2021 doi: 10.1111/ner.13457 [published Online First: 2021/05/20]
18. Bendixen M, Jørgensen OD, Kronborg C, et al. Postoperative pain and quality of life after lobectomy via video-assisted thoracoscopic surgery or anterolateral thoracotomy for early stage lung cancer: a randomised controlled trial. *The Lancet Oncology* 2016;17(6):836-44. doi: 10.1016/s1470-2045(16)00173-x [published Online First: 2016/05/11]
19. Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *The Cochrane database of systematic reviews* 2019;10:Ed000142. doi: 10.1002/14651858.Ed000142 [published Online First: 2019/10/24]
20. Ochoa JL. Neuropathic pain: redefinition and a grading system for clinical and research purposes. *Neurology* 2009;72(14):1282-3. doi: 10.1212/01.wnl.0000346325.50431.5f [published Online First: 2009/04/08]
21. Brazier JE, Harper R, Jones NM, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ (Clinical research ed)* 1992;305(6846):160-4. doi: 10.1136/bmj.305.6846.160 [published Online First: 1992/07/18]
22. McGowan J, Sampson M, Salzwedel DM, et al. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. *Journal of clinical epidemiology* 2016;75:40-6. doi: 10.1016/j.jclinepi.2016.01.021 [published Online First: 2016/03/24]
23. Huang X, Lin J, Demner-Fushman D. Evaluation of PICO as a knowledge representation for clinical questions. *AMIA Annual Symposium proceedings AMIA Symposium* 2006;2006:359-63. [published Online First: 2007/01/24]
24. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *Journal of clinical epidemiology* 2011;64(4):383-94. doi: 10.1016/j.jclinepi.2010.04.026 [published Online First: 2011/01/05]
25. Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014;14:135. doi: 10.1186/1471-2288-14-135 [published Online First: 20141219]
26. Shi J, Luo D, Wan X, et al. Detecting the skewness of data from the sample size and the five-number summary. 2020
27. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ (Clinical research ed)* 1997;315(7109):629-34. doi: 10.1136/bmj.315.7109.629 [published Online First: 1997/10/06]
28. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ (Clinical research ed)* 2011;343:d4002. doi: 10.1136/bmj.d4002 [published Online First: 2011/07/26]
29. Li H, Ding Y, Zhu Y, et al. Effective Treatment of Postherpetic Neuralgia at the First Branch of the Trigeminal Nerve by High-Voltage Pulsed Radiofrequency. *Frontiers in neurology*

346 2021;12:746035. doi: 10.3389/fneur.2021.746035 [published Online First: 2021/10/29]

347

**Supplement 1.** PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

| Section and topic | Item No | Checklist item | Check results |
|---|---|---|---|
| **ADMINISTRATIVE INFORMATION** | | | |
| Title: | | | |
| Identification | 1a | Identify the report as a protocol of a systematic review | Yes |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such | Yes |
| Registration | 2 | If registered, provide the name of the registry (such as PROSPERO) and registration number | Yes |
| Authors: | | | |
| Contact | 3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author | Yes |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review | Yes |
| Amendments | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | Yes |
| Support: | | | |
| Sources | 5a | Indicate sources of financial or other support for the review | Yes |
| Sponsor | 5b | Provide name for the review funder and/or sponsor | Yes |
| Role of sponsor or funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | Yes |

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| **INTRODUCTION** | | | |
| Rationale | 6 | Describe the rationale for the review in the context of what is already known | Yes |
| Objectives | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | Yes |
| **METHODS** | | | |
| Eligibility criteria | 8 | Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review | Yes |
| Information sources | 9 | Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage | Yes |
| Search strategy | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | Yes |
| Study records: | | | |
| Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | Yes |
| Selection process | 11b | State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) | Yes |
| Data collection process | 11c | Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | Yes |
| Data items | 12 | List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications | Yes |
| Outcomes and prioritization | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | Yes |

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| Risk of bias in individual studies | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | Yes |
| Data synthesis | 15a | Describe criteria under which study data will be quantitatively synthesized | Yes |
| | 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$, Kendall's $\tau$) | Yes |
| | 15c | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) | Yes |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned | Yes |
| Meta-bias(es) | 16 | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) | Yes |
| Confidence in cumulative evidence | 17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) | Yes |

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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| Search step | Search terms |
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# Efficacy and safety of high-voltage pulsed radiofrequency ablation versus standard-voltage pulsed radiofrequency ablation for patients with neuropathic pain: protocol for a systematic review and meta-analysis



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# Efficacy and safety of high-voltage pulsed radiofrequency ablation versus standard-voltage pulsed radiofrequency ablation for patients with neuropathic pain: protocol for a systematic review and meta-analysis

[1,2]Yitong Jia, [3]Zheng Wang, [1,2]Yanhui Ma, [4]Tengteng Wang, [1,2]Kunpeng Feng, [1,2]Guang Feng [1,2]Tianlong Wang

[1]Department of Anesthesiology, Xuanwu Hospital, Capital Medical University, Beijing, China.
[2]Beijing Municipal Geriatric Medical Research Center, Beijing, China.
[3]Department of General Surgery, Xuanwu Hospital, Capital Medical University, Beijing, China.
[4]Department of Thoracic surgery, Xuanwu Hospital, Capital Medical University, Beijing, China.

Correspondence to
Prof Tianlong Wang, Department of Anesthesiology, Xuanwu Hospital, Capital Medical University, Beijing, China; E-mail: w_tl5595@hotmail.com.

Yitong Jia, Zheng Wang and Yanhui Ma contributed equally to this paper.

## Abstract

**Introduction** Pulsed radiofrequency (PRF) ablation is commonly used for the treatment of neuropathic pain (NP). However, it is unclear whether increasing the output voltage of PRF can safely improve its efficacy. This study aims to compare the efficacy and safety of high-voltage PRF ablation and standard-voltage PRF ablation for the treatment of patients with NP.

**Methods and analysis** We will search PubMed/MEDLINE, EMBASE, Web of Science, the Cochrane Library, conference proceedings for relevant abstracts, clinical trials registers (ClinicalTrials.gov), and the World Health Organization's International Clinical Trial Registry Platform (WHO ICTRP) (from the date of inception until March 15, 2022). Only randomized controlled trials (RCTs)will be included. Two reviewers (YJ and GF) will independently perform study screening and selection, data extraction, risk of bias assessment, and quality of evidence assessment. The primary outcome of this meta-analysis will be the efficiency rate in patients with NP. The secondary outcomes will include numeric rating scale score, visual analog scale score, time to take effect, rescue drug dosage, quality of life using the health questionnaire (SF-36), and the incidence of adverse events. Meta-analyses will be conducted using standard meta-analysis software (RevMan V.5.3, The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark).

**Ethics and dissemination** The requirement for ethical approval was waived as our systematic review will be based on published literature. The results of this study will be submitted to a peer-reviewed journal.

**PROSPERO registration number** CRD42022297804.


**Strengths and limitations of this study**

To the best of our knowledge, this will be the first systematic review and meta-analysis to evaluate the efficacy and safety of high-voltage PRF ablation for the treatment of patients with NP. To provide unbiased information, only RCTs will be included.

The study findings will provide comprehensive information for future study designs in terms of interventional treatment of neuropathic pain.

The accuracy of our research conclusions might be subjected to language limitations as only studies published in English will be included.

**Key words:** high-voltage, pulsed radiofrequency, neuropathic pain, randomized

controlled trials

## Introduction

Neuropathic pain (NP) is a common chronic pain condition caused by lesions or diseases affecting the somatosensory nervous system, including trigeminal neuralgia, peripheral nerve injury pain, painful polyneuropathy, post herpetic neuralgia, and central post stroke pain.[1] Epidemiological data have reported that the global prevalence of NP is approximately 6.9% - 10%.[2] Neuropathic pain is a refractory pain syndrome with a long duration of occurrence, frequent recurrent attacks, and poor response to traditional analgesics. Most patients with NP suffer from ongoing or intermittent spontaneous pain accompanied by burning, pricking, and squeezing sensations, and have a poor quality of life (QoL).[3] Therefore, finding an effective treatment option for NP and improving patients' QoL is of great importance.

In recent years, pulsed radiofrequency (PRF) ablation, a new type of neuromodulation technique, has been successfully applied in the treatment of NP.[4-9] Different from continuous radiofrequency (CRF), which produces heat by friction and vibration, leading to thermocoagulation, denaturation, and necrosis of the target tissue[10 11], PRF provides pulsed energy waves followed by a 480-ms heat dissipation interval, and the temperature does not exceed 42°C.[12-14] PRF treatment exerts its effect via the modulation of nerve function ， which is a result of the electric field effect and not the impedance of pain signal transduction;[15 16] thus, PRF ablation is a nondestructive technique that can be repeatedly applied without causing nerve tissue damage.

The standard proposed PRF parameters are set as follows: an output voltage of 45 V, temperature of 42°C, pulse frequency of 2 Hz, output frequency of 500 kHz, continuous current action of 20 ms, and intermission period of 480 ms. Recently, scholars have attempted to treat patients with NP using high-voltage PRF ablation. Teixeira and Sluijter first reported that a high-voltage PRF ablation of 60 V used to treat patients with discogenic pain attained satisfactory efficacy that lasted over 3 months.[17] In 2013, Luo et al found that the postoperative numeric rating scale (NRS) score had a significant negative correlation with the output voltage of PRF.[18] Afterwards, Luo et al compared the efficacy of high-voltage PRF with standard-voltage PRF for idiopathic trigeminal neuralgia (TN) patients who responded poorly to oral carbamazepine or nerve blockade by steroid, and the results revealed the 1- year effective rate of high-voltage PRF (69%) was significantly higher than that in the standard-voltage PRF treatment(19%) (P = 0.000). [19]Additionally, they compared the efficacy of high voltage PRF and standard voltage PRF for refractory neuralgia infraorbital nerve therapy, and reported that high voltage PRF ablation could achieve higher response rates at 1 month, 3 months, 6 months, and 1 year post-procedure.[20] Jia et al retrospectively analyzed the medical data of patients with idiopathic TN undergoing PRF. The study found that for patients who did not respond to the first PRF treatment and underwent the second PRF treatment, a higher dose of out-put voltage than the initial one could achieve improved analgesic effect[21-23].

However, the number of patients who experienced mild numbness postoperatively was greater in the high-voltage group (27%) than in the standard-voltage group (13%).[20] In

addition, a randomized controlled trial (RCT) conducted by Wan et al showed that the scores were significantly lower in the high-voltage group than in the standard-voltage group at 3 and 6 months; however, no significant difference was observed at 1 month after treatment.[24] A study by Wan et al revealed that the incidence of ecchymoses in the high-voltage group (19.2%) was higher than that in the standard-voltage group (12.1%). As a result, further analysis is required to determine whether the efficacy of high-voltage PRF ablation at different time points is superior to that of standard-voltage PRF ablation, and whether high-voltage PRF ablation is a safe treatment method for NP.

The primary objectives of this study will be to compare the efficacy and safety of high-voltage PRF ablation and standard-voltage PRF ablation for the treatment of NP at different time points postoperatively through a systematic review and meta-analysis of RCTs.

# Methods

This protocol was developed according to the reporting guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement[25] **(checklist in Supplement 1).** The protocol for this systematic review was registered in the PROSPERO database (registration number: CRD42022297804). Our systematic review will be conducted in accordance with the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions.[26] Any amendments made to this protocol and the whole review process will be updated in a timely manner on the

PROSPERO registration and the final manuscript.

## Criteria for considering eligible studies

### Types of studies

Only RCTs will be included. All studies must be published in English. Experimental animal studies will be excluded.

### Participants

Patients with NP conditions recognized and defined by the International Association for the Study of Pain (IASP)[27] will be included. Neuropathic pain is initiated or caused by a primary lesion or dysfunction of the nervous system. Studies regarding diabetic neuropathy, complex regional pain syndrome type I, low back pain without radicular pain, and postsurgical pain will be excluded.

### Interventions and Comparators

We will examine trials investigating high-voltage PRF treatment for patients with NP. The high-voltage PRF treatment will be set to the manual pulse mode: the initial voltage will be 40 or 45 V, and the output voltage will then be gradually increased to the highest voltage the patient can tolerate (temperature control below 50°C). The comparator will be the standard PRF treatment.

### Outcome measures

The primary outcome of this meta-analysis is the efficiency rate in patients with NP. The predefined time points for the efficiency rate will be 1 month, 3 months, and 6 months after the procedure. Additionally, 1-year or 2-year time point will also be considered. Treatment efficiency recurrence is defined as a pain reduction of greater than 50% after treatment compared to pre-surgery. Secondary outcomes will include (NRS) or visual analog scale (VAS) score, time to take effect, rescue drug dosage, quality of life (QoL) determined using a health questionnaire (SF-36)[28] at 1 month, 3 months, and 6 months postoperatively, and incidence of adverse events (AEs).

## Information sources and search strategy

A computer-based search strategy will be designed by an experienced librarian and revised by another expert librarian according to the Peer Review of Electronic Search Strategies checklist.[29] The primary source of literature will be the following major electronic databases: PubMed/MEDLINE, EMBASE, Web of Science, and the Cochrane Library (from the date of inception until March 15, 2022). The secondary source of potentially relevant research includes conference proceedings for relevant abstracts, clinical trials registers (ClinicalTrials.gov), and the World Health Organization's International Clinical Trial Registry Platform (WHO ICTRP) to identify ongoing studies. The search will encompass a broad range of terms and keywords related to "high-voltage," "pulsed radiofrequency," "neuropathic pain," and "RCT". The detailed search strategy is

presented in **Supplement 2.**

## Data selection and analysis

### Study Selection

We will use the Population, Intervention, Comparison, Outcome (PICO) model[30]to determine the specific criteria for selecting studies. Two reviewers (YJ and GF) will independently screen and select the relevant studies. During the initial screening, reviewers will determine whether the study could be included by screening the titles and abstracts retrieved via database search. We will screen the full texts retained from the initial selection of articles to include studies that meet the eligibility criteria. Disagreements between the two reviewers will be resolved by a third reviewer (TW). If several studies present data from the same study population or multiple publications from the same study are published in chronological order, the study with the most direct interventions or the largest sample size will be selected. The same methods will be used for citation, reference screening, and selection, as well as for protocols registered in clinical trial registries.

## Data extraction

A standardized electronic form for data extraction will be created by ZW. Two reviewers (YJ and GF) will independently extract the following data: study characteristics (e.g., name of the first author, year of publication, type of study, sample size), population

characteristics (e.g., age, gender, disease duration, medical history, preoperative pain intensity, and follow-up period), and outcome data (e.g., primary and secondary outcomes and any AEs caused by PRF treatment). Similarly, a third reviewer will be required to resolve any discrepancies. We will attempt to contact the study authors by email or post for further information in case of any ambiguity or insufficient information. Table 1 presents the characteristics of the studies that will be included.

## Assessment of risk of bias and quality of evidence assessment

Two reviewers (YJ and GF) will independently assess the risk of bias (RoB) and a third reviewer (ZW) will resolve discrepancies. The RoB of RCTs will be assessed according to items in the Cochrane Collaboration's tool.[26]

We will evaluate the overall quality of the body of evidence in accordance with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology,[31] which examines study design, RoB, inconsistency, indirectness, and imprecision. Accordingly, quality of evidence will be rated as high, moderate, low, or very low.

## Data synthesis and analysis

Meta-analyses will be conducted using the standard meta-analysis software (RevMan V.5.3, The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark). We will compute standardized mean differences (SMDs) and 95% confidence

intervals (CIs) for continuous outcomes, and risk ratios (RR) with 95% CI for binary outcomes. A two-tailed p-value < 0.05 will be considered statistically significant. We will assess the intervention effects between high-voltage PRF and standard-voltage PRF using pre- to post-intervention changes. When the data in the literature are expressed as median values and quartiles, we will use mathematical operations to transform them into mean and standard deviation (SD).[32 33] Additionally, we will use forest plots to visualize pooled estimates and the extent of heterogeneity among studies. Heterogeneity will be assessed using the $I^2$ statistic. $I^2 > 50\%$ is an indication of substantial heterogeneity, and in such cases the random-effects model will be used to analyze the outcomes; otherwise, a fixed-effect model will be applied. If heterogeneity is observed, we will perform subgroup analysis according to prespecified variables, such as study design, intervention characteristics, or RoB. The sources of heterogeneity will be explored using sensitivity analysis. A funnel plot[34] or Egger test[35] will be used to assess publication bias.

## Patient and Public Involvement

Since our study is a systematic review based on published literature, no patients will be involved.

# Discussion

Our study aims to compare the efficacy and safety of high-voltage PRF ablation and

standard-voltage PRF ablation for NP therapy and provide clinical evidence for the selection of PRF modes in clinical practice via synthesizing RCTs in journal publications. This study has some limitations. The sample size of the eligible RCTs might not be large and the accuracy of our research conclusions might be biased due to language limitations, as we will only include studies published in English. Overall, the study findings will provide comprehensive information for future study designs in terms of interventional treatment of NP.

## Abbreviations

PRF, Pulsed radiofrequency; NP, neuropathic pain; RCTs, randomized controlled trials; NRS, numeric rating scale; VAS, visual analog scale; QoL, quality of life; AEs, adverse events; RoB, risk of bias; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; SMDs, standardized mean differences; CIs, confidence intervals; RR, risk ratios.

## Ethics and dissemination

Ethical approval was waived as our systematic review will be based on published literature. The results of this study will be submitted to a peer-reviewed journal.

**Acknowledgments** The authors would like to thank the participants of the study for their cooperation.

**Contributors** YJ, ZW, TW and TW made substantial contributions to clinical study design; YJ, YM and GF made substantial contributions to manuscript preparation, editing and review; KF made contributions to English language editing; YM, KF and GF consulted about clinical issues; YJ, YM, TW and TW have given final approval of the version to be published. YJ, ZW and YM contributed equally to this work. TW is responsible as corresponding author.

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**Consent for publication** All authors consented.

**Conflicts of interest** None.

# References

1. Baron R, Binder A, Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. *The Lancet Neurology* 2010;9(8):807-19. doi: 10.1016/s1474-4422(10)70143-5 [published Online First: 2010/07/24]

2. van Hecke O, Austin SK, Khan RA, et al. Neuropathic pain in the general population: a systematic review of epidemiological studies. *Pain* 2014;155(4):654-62. doi: 10.1016/j.pain.2013.11.013 [published Online First: 2013/12/03]

3. Colloca L, Ludman T, Bouhassira D, et al. Neuropathic pain. *Nature reviews Disease primers* 2017;3:17002. doi: 10.1038/nrdp.2017.2 [published Online First: 2017/02/17]

4. Park CH, Lee SH, Lee PB. Intradiscal Pulsed Radiofrequency Application Duration Effect on Lumbar Discogenic Low Back Pain. *Pain physician* 2020;23(5):E535-e40. [published Online First: 2020/09/25]

5. Martin DC, Willis ML, Mullinax LA, et al. Pulsed radiofrequency application in the treatment of chronic pain. *Pain practice : the official journal of World Institute of Pain* 2007;7(1):31-5.

doi: 10.1111/j.1533-2500.2007.00107.x [published Online First: 2007/02/20]

6. Kim K, Jo D, Kim E. Pulsed Radiofrequency to the Dorsal Root Ganglion in Acute Herpes Zoster and Postherpetic Neuralgia. *Pain physician* 2017;20(3):E411-e18. [published Online First: 2017/03/25]

7. Shi Y, Wu W. Treatment of Neuropathic Pain Using Pulsed Radiofrequency: A Meta-analysis. *Pain physician* 2016;19(7):429-44. [published Online First: 2016/09/28]

8. Jia Y, Shrestha N, Wang X, et al. The Long-Term Outcome of CT-Guided Pulsed Radiofrequency in the Treatment of Idiopathic Glossopharyngeal Neuralgia: A Retrospective Multi-Center Case Series. *Journal of pain research* 2020;13:2093-102. doi: 10.2147/jpr.S259994 [published Online First: 2020/09/10]

9. Vuka I, Marciuš T, Došenović S, et al. Efficacy and Safety of Pulsed Radiofrequency as a Method of Dorsal Root Ganglia Stimulation in Patients with Neuropathic Pain: A Systematic Review. *Pain medicine (Malden, Mass)* 2020;21(12):3320-43. doi: 10.1093/pm/pnaa141 [published Online First: 2020/06/04]

10. Ren H, Zhao C, Wang X, et al. The Efficacy and Safety of the Application of Pulsed Radiofrequency, Combined With Low-Temperature Continuous Radiofrequency, to the Gasserian Ganglion for the Treatment of Primary Trigeminal Neuralgia: Study Protocol for a Prospective, Open-Label, Parall. *Pain physician* 2021;24(1):89-97. [published Online First: 2021/01/06]

11. Contreras Lopez WO, Navarro PA, Vargas MD, et al. Pulsed Radiofrequency Versus Continuous Radiofrequency for Facet Joint Low Back Pain: A Systematic Review. *World*

*neurosurgery* 2019;122:390-96. doi: 10.1016/j.wneu.2018.10.191 [published Online First: 2018/11/08]

12. Wu CY, Lin HC, Chen SF, et al. Efficacy of Pulsed Radiofrequency in Herpetic Neuralgia: A Meta-Analysis of Randomized Controlled Trials. *The Clinical journal of pain* 2020;36(11):887-95. doi: 10.1097/ajp.0000000000000867 [published Online First: 2020/07/24]

13. Wu H, Zhou J, Chen J, et al. Therapeutic efficacy and safety of radiofrequency ablation for the treatment of trigeminal neuralgia: a systematic review and meta-analysis. *Journal of pain research* 2019;12:423-41. doi: 10.2147/jpr.S176960 [published Online First: 2019/01/31]

14. Li H, Ding Y, Zhu Y, et al. Effective Treatment of Postherpetic Neuralgia at the First Branch of the Trigeminal Nerve by High-Voltage Pulsed Radiofrequency. *Frontiers in neurology* 2021;12:746035. doi: 10.3389/fneur.2021.746035 [published Online First: 2021/10/29]

15. Sam J, Catapano M, Sahni S, et al. Pulsed Radiofrequency in Interventional Pain Management: Cellular and Molecular Mechanisms of Action - An Update and Review. *Pain physician* 2021;24(8):525-32. [published Online First: 2021/11/19]

16. Vanneste T, Van Lantschoot A, Van Boxem K, et al. Pulsed radiofrequency in chronic pain. *Current opinion in anaesthesiology* 2017;30(5):577-82. doi: 10.1097/aco.0000000000000502 [published Online First: 2017/07/13]

17. Teixeira A, Sluijter ME. Intradiscal high-voltage, long-duration pulsed radiofrequency for discogenic pain: a preliminary report. *Pain medicine (Malden, Mass)* 2006;7(5):424-8. doi:

10.1111/j.1526-4637.2006.00138.x [published Online First: 2006/10/04]

18. Luo F, Meng L, Wang T, et al. Pulsed radiofrequency treatment for idiopathic trigeminal neuralgia: a retrospective analysis of the causes for ineffective pain relief. *European journal of pain (London, England)* 2013;17(8):1189-92. doi: 10.1002/j.1532-2149.2012.00278.x [published Online First: 2013/01/17]

19. Fang L, Tao W, Jingjing L, et al. Comparison of High-voltage- with Standard-voltage Pulsed Radiofrequency of Gasserian Ganglion in the Treatment of Idiopathic Trigeminal Neuralgia. *Pain practice : the official journal of World Institute of Pain* 2015;15(7):595-603. doi: 10.1111/papr.12227 [published Online First: 2014/06/24]

20. Luo F, Wang T, Shen Y, et al. High Voltage Pulsed Radiofrequency for the Treatment of Refractory Neuralgia of the Infraorbital Nerve: A Prospective Double-Blinded Randomized Controlled Study. *Pain physician* 2017;20(4):271-79. [published Online First: 2017/05/24]

21. Fang L, Jia Z. In Response to Comments on "Long-term Follow-up of Pulsed Radiofrequency Treatment for Trigeminal Neuralgia: Kaplan-Meier Analysis in a Consecutive Series of 149 Patients". *Pain physician* 2022;25(2):E409. [published Online First: 2022/03/25]

22. Silva V. Comments on "Long-term Follow-up of Pulsed Radiofrequency Treatment for Trigeminal Neuralgia: Kaplan-Meier Analysis in a Consecutive Series of 149 Patients". *Pain physician* 2022;25(2):E408. [published Online First: 2022/03/25]

23. Zipu J, Hao R, Chunmei Z, et al. Long-term Follow-up of Pulsed Radiofrequency Treatment for Trigeminal Neuralgia: Kaplan-Meier Analysis in a Consecutive Series of 149 Patients.

*Pain physician* 2021;24(8):E1263-e71. [published Online First: 2021/11/19]

24. Wan CF, Song T. Comparison of Two Different Pulsed Radiofrequency Modes for Prevention of Postherpetic Neuralgia in Elderly Patients with Acute/Subacute Trigeminal Herpes Zoster. *Neuromodulation : journal of the International Neuromodulation Society* 2021 doi: 10.1111/ner.13457 [published Online First: 2021/05/20]

25. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ (Clinical research ed)* 2016;354:i4086. doi: 10.1136/bmj.i4086 [published Online First: 2016/07/23]

26. Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *The Cochrane database of systematic reviews* 2019;10:Ed000142. doi: 10.1002/14651858.Ed000142 [published Online First: 2019/10/24]

27. Ochoa JL. Neuropathic pain: redefinition and a grading system for clinical and research purposes. *Neurology* 2009;72(14):1282-3. doi: 10.1212/01.wnl.0000346325.50431.5f [published Online First: 2009/04/08]

28. Brazier JE, Harper R, Jones NM, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ (Clinical research ed)* 1992;305(6846):160-4. doi: 10.1136/bmj.305.6846.160 [published Online First: 1992/07/18]

29. McGowan J, Sampson M, Salzwedel DM, et al. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. *Journal of clinical epidemiology* 2016;75:40-6. doi: 10.1016/j.jclinepi.2016.01.021 [published Online First: 2016/03/24]

30. Huang X, Lin J, Demner-Fushman D. Evaluation of PICO as a knowledge representation for clinical questions. *AMIA Annual Symposium proceedings AMIA Symposium* 2006;2006:359-63. [published Online First: 2007/01/24]

31. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *Journal of clinical epidemiology* 2011;64(4):383-94. doi: 10.1016/j.jclinepi.2010.04.026 [published Online First: 2011/01/05]

32. Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014;14:135. doi: 10.1186/1471-2288-14-135 [published Online First: 20141219]

33. Shi J, Luo D, Wan X, et al. Detecting the skewness of data from the sample size and the five-number summary. 2020

34. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ (Clinical research ed)* 1997;315(7109):629-34. doi: 10.1136/bmj.315.7109.629 [published Online First: 1997/10/06]

35. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ (Clinical research ed)* 2011;343:d4002. doi: 10.1136/bmj.d4002 [published Online First: 2011/07/26]

Table 1 Main characteristics of RCTs comparing the efficacy and safety of high-voltage PRF and standard-voltage PRF for the treatment of NP

| Study ID | Sample size | Types of neuropathic pain | Setting | Duration | Number of female (%)/ male (%) patients | Age (years) | Preoperative pain (VAS/ NRS) | Preoperative QoL | Postoperative pain (VAS/ NRS) | Postoperative QoL | Complications |
|---|---|---|---|---|---|---|---|---|---|---|---|
| A | | | | | | | | | | | |
| B | | | | | | | | | | | |
| C | | | | | | | | | | | |
| …… | | | | | | | | | | | |

Abbreviations: RCT, randomized controlled trials; VAS: visual analog scale; NRS: numeric rating scale; QoL: quality of life.

**Supplement 1.** PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

| Section and topic | Item No | Checklist item | Page No |
|---|---|---|---|
| **ADMINISTRATIVE INFORMATION** | | | |
| Title: | | | |
| Identification | 1a | Identify the report as a protocol of a systematic review | 1 |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such | n/a |
| Registration | 2 | If registered, provide the name of the registry (such as PROSPERO) and registration number | 2 |
| Authors: | | | |
| Contact | 3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author | 1 |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review | 11 |
| Amendments | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | n/a |
| Support: | | | |
| Sources | 5a | Indicate sources of financial or other support for the review | 11 |
| Sponsor | 5b | Provide name for the review funder and/or sponsor | 11 |
| Role of sponsor or funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | 11 |

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| **INTRODUCTION** | | | |
| Rationale | 6 | Describe the rationale for the review in the context of what is already known | 3 |
| Objectives | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | 3-4 |
| **METHODS** | | | |
| Eligibility criteria | 8 | Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review | 5 |
| Information sources | 9 | Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage | 6-7 |
| Search strategy | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | 6-7 |
| Study records: | | | |
| Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | 7 |
| Selection process | 11b | State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) | 7 |
| Data collection process | 11c | Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | 7 |
| Data items | 12 | List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications | 9 |
| Outcomes and prioritization | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | 6 |

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| Risk of bias in individual studies | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | 8 |
| Data synthesis | 15a | Describe criteria under which study data will be quantitatively synthesized | 9 |
| | 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$, Kendall's $\tau$) | 9 |
| | 15c | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) | 9 |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned | 9 |
| Meta-bias(es) | 16 | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) | 8 |
| Confidence in cumulative evidence | 17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) | 8 |

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

*From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.*

| Search step | Search terms |
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| #1 | "neuralgia"[MeSH Terms] OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR "neuralgias"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("neuropathic"[All Fields] AND "pain"[All Fields]) OR "neuropathic pain"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("neuropathic"[All Fields] AND "pains"[All Fields]) OR "neuropathic pains"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("pain"[All Fields] AND "neuropathic"[All Fields]) OR "pain neuropathic"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("pains"[All Fields] AND "neuropathic"[All Fields]) OR "pains neuropathic"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR "neurodynia"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("neuralgia"[All Fields] AND "atypical"[All Fields]) OR "neuralgia atypical"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("atypical"[All Fields] AND "neuralgia"[All Fields]) OR "atypical neuralgia"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("atypical"[All Fields] AND "neuralgias"[All Fields]) OR "atypical neuralgias"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("neuralgias"[All Fields] AND "atypical"[All Fields]) OR "neuralgias atypical"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("neuralgia"[All Fields] AND "iliohypogastric"[All Fields] AND "nerve"[All Fields])) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("iliohypogastric"[All Fields] AND "nerve"[All Fields] AND "neuralgia"[All Fields])) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("iliohypogastric"[All Fields] AND "nerve"[All Fields] AND "neuralgias"[All Fields])) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("nerve"[All Fields] AND "neuralgia"[All Fields] AND "iliohypogastric"[All Fields])) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("nerve"[All Fields] AND "neuralgias"[All Fields] AND "iliohypogastric"[All Fields])) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("neuralgias"[All Fields] AND "iliohypogastric"[All Fields] AND "nerve"[All Fields])) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("paroxysmal"[All Fields] AND "nerve"[All Fields] AND "pain"[All Fields]) OR "paroxysmal nerve pain"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("nerve"[All Fields] AND "pain"[All Fields] AND "paroxysmal"[All Fields])) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("nerve"[All Fields] AND "pains"[All Fields] AND "paroxysmal"[All Fields])) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("pain"[All Fields] AND "paroxysmal"[All Fields] AND "nerve"[All Fields])) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("pains"[All Fields] AND "paroxysmal"[All Fields] AND "nerve"[All Fields])) OR |

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| #3 | (clinical[tiab] AND trial[tiab]) OR "clinical trials as topic"[mesh] OR "clinical trial"[pt] OR random*[tiab] OR "random allocation"[mesh] OR "therapeutic use"[sh] |
| #4 | #1 AND #2 AND #3 |